

A further explanation, though mainly conjectural, is worthy of consideration. Before anti-D immunoglobulin was available it was not uncommon to encounter Rh-negative women who formed Rh-antibodies, but the titres remained low and they had only mildly affected infants. Possibly anti-D immunoglobulin can suppress "good" responders but not these low responders. Undoubtedly there is a point of no return, as was seen in the case outlined above: although anti-D was given the mother's second and third child both succumbed to the Rh antibodies.

The simplest explanation of why anti-D immunoglobulin protects at all is that by destroying fetal Rh (D)-positive cells it reduces the length of time the Rh antigen is exposed to potentially anti-D producing lymphocytes. This concept seems to be supported by the recent work of Woodrow *et al.*¹³ They injected Rh (D)-negative Kell-negative volunteers with D-positive Kell-positive red cells and then gave anti-Kell antibodies. They showed a reduction in the incidence of Rh antibodies. This is not, however, the only possibility.¹⁴ The suppression of anti-D may be a more complex immunological mechanism. Certainly our results suggest that the future immunological response may be altered by the administration of anti-D and also support the view that the mechanism of anti-D protection is more complex than would be expected if it were simply a matter of removal of fetal Rh-positive cells.

We acknowledge the help of the consultant obstetricians and paediatricians in the region, particularly, Professor J S Scott, professor of obstetrics and gynaecology, University of Leeds, and we thank Mr W K Haggas for the statistical analysis of our results.

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Idiopathic heart block: association with vitiligo, thyroid disease, pernicious anaemia, and diabetes mellitus

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British Medical Journal, 1975, 4, 322-324

Summary

Out of 100 patients with chronic heart block 16 had one or more autoimmune disorders—namely, vitiligo (5), hypothyroidism (4), Graves's disease (1), pernicious anaemia (2), and diabetes mellitus (9). All these disorders occurred with greater frequency than normal and were more prevalent than in a group of hospital inpatients of comparable age. Autoantibodies were not increased. We suggest that among patients with idiopathic heart block there is a subgroup with multiple autoimmune disorders.

Introduction

In most cases of chronic heart block the aetiology is unknown. The commonest finding at necropsy is end-stage fibrosis of the bundle of His and its branches.^{1,2} Complete heart block has occasionally been described in thyroid disorders, including primary myxoedema³ and thyrotoxicosis.⁴ This study was instituted to assess the frequency of thyroid disease in patients with chronic heart block. In view of the autoimmune aetiology of most cases of primary hypothyroidism, together with the known associations between lymphomatous thyroiditis, pernicious anaemia, vitiligo, Addison's disease, and diabetes mellitus,⁵ the prevalence of these disorders was also determined. The serum of all patients studied was screened for organ-specific and non-organ-specific autoantibodies.

Subjects and Methods

One hundred consecutive patients with chronic heart block admitted to hospital for pacemaker implantation were studied. (Patients with acute heart block—for example, after myocardial infarction—were not included.) Altogether 49 were men and 51 women and their ages ranged from 33 to 96 years (mean 72.4 years) (table I). The duration of their disease, as judged by the time from the onset of symptoms, was 3 months to 23 years (mean 6 years). A detailed personal and family history was taken and the patients were examined for any known cause of heart block and for the presence of vitiligo, thyroid disease, diabetes, or pernicious anaemia. Biochemical screening included haemoglobin, erythrocyte sedimentation rate, urea and electrolytes, Wassermann reaction (W.R.), calcium, phosphate and alkaline phosphatase, plasma proteins, serum thyroxine and Thyopac-3 index, and, when appropriate, serum vitamin B₁₂ level. In 40 patients immunoglobulin levels were determined. Sera were collected and stored at -20°C and tested by us within three months.

Controls.—One hundred healthy people matched for age and sex with the heart-block patients were selected from a larger group tested at the Middlesex Hospital. They consisted of residents in old people's homes and, for the younger age groups, friends of rheumatoid arthritis patients who had accompanied them to hospital.

Serological Methods.—Autoantibodies were detected by a standard sandwich immunofluorescence technique using rabbit antihuman FAB conjugated with fluorescein isothiocyanate. Sera were tested at a 1/10 dilution on human thyroid and stomach and on rat liver and kidney sections.⁶ Thyroid microsomal antibodies were titrated by the Fujizoki haemagglutination test, and thyroglobulin antibody was detected by tanned red cell haemagglutination (T.R.C.).

Results

Of the 100 cases of chronic heart block 85 were clinically idiopathic and in 15 a possible cause coexisted, including ischaemic heart disease, calcific aortic valve disease, and Paget's disease. Sixteen patients had diseases associated with organ-specific autoimmunity and three had multiple disorders (table II). All had chronic heart block of unknown

TABLE I—Age Distribution of 100 Patients with Chronic Heart Block

										Age Group in Years										Total					
										30–	35–	40–	45–	50–	55–	60–	65–	70–	75–	80–	85–	90–	95–		
No. of men				1	1	2	3	4	10	9	10	6	2	1	1	49
No. of women	1			1	1	1		1	10	9	13	9	3	2		51

TABLE II—Prevalence of Disorders Associated with Organ-specific Autoimmunity in 100 Patients with Chronic Heart Block

Disease	No. of Cases		% Expected Prevalence in Comparable Age Groups	P
	M.	F.		
Vitiligo	3	2	1.4 ¹⁹	0.01
Primary hypothyroidism	1	3	1.6 ¹⁸	0.05
Hyperthyroidism	..	1	0.5 ¹⁸	N.S.
Pernicious anaemia	1	1	0.1–0.3 ^{16, 17}	0.005–0.04
Diabetes mellitus:				
Insulin-dependent	..	2	3.0–6.0 ²²	0.004–0.15
Non-insulin-dependent	4	3		

N.S. = Not significant.

TABLE III—Serological Results in 100 Cases of Chronic Heart Block and 100 Controls Matched for Age and Sex

Type of Antibodies	Percentage Positive	
	Heart-block Cases	Healthy Controls
Thyroid { Microsomal	15 (10 ⁴ –80 ⁴)	11
Thyroglobulin	13 (T.R.C. 10–1280)	7
Gastric parietal cell	8 (10–40)	13
Antinuclear (A.N.A.)	22 (10–160)	15
Mitochondrial (A.M.A.)	2 (60–640)	0
Smooth muscle	4	5

Figures in parentheses indicate range of haemagglutination titres for microsomal (Fujizaki test) and thyroglobulin antibodies (Burrroughs Wellcome tanned red cell test). A.N.A. and A.M.A. titres were obtained by immunofluorescence.

aetiology except for one patient with non-insulin-dependent diabetes, in whom a definite history of ischaemic heart disease may have contributed to damage of the conducting system. One additional patient was on vitamin B₁₂ replacement for post-gastrectomy megaloblastic anaemia, and two others had a positive family history of pernicious anaemia. The following case history illustrates one of the patients with multiple autoimmunity.

A 76-year-old man had developed vitiligo in adolescence and pernicious anaemia at age 45. In 1973 (age 74) he had acute pancreatitis; his pulse was normal during his stay in hospital. In August 1974 he suffered Adams-Stokes attacks and complete heart block was documented. At the time he was clinically euthyroid, but six months later he complained of intolerance to cold and of a general slowing down. There was no family history of autoimmune disorder. Examination showed extensive vitiligo and early hypothyroidism. There were no signs of diabetes mellitus.

Investigations were: E.C.G., complete heart block, rate 16/min, mean axis 0°, QRS 0.16 s with right bundle-branch-block pattern; chest x-ray film, moderately enlarged heart; haemoglobin 16 g/dl; blood W.R. negative; glucose tolerance normal; serum thyroxine 37 nmol/l (2.9 µg/100 ml); Thyropac-3 index 103; serum thyrotrophin 50 mU/l; ¹³¹I uptake (4 hours) 13%; triiodothyronine 1.5 nmol/l (1 ng/ml); immunoglobulins normal; autoantibodies positive for thyroid cytoplasm, gastric parietal cells, and pancreatic endocrine cells by immunofluorescence;⁷ thyroglobulin T.R.C. titre 1280; Fujizaki haemagglutination titre 80²; intrinsic factor antibody positive.

Two other patients had multiple autoimmune disorders—a 61-year-old woman with heart block, pernicious anaemia, hypothyroidism, and insulin-dependent diabetes; and a 68-year-old man with vitiligo, heart block, and diabetes mellitus.

The serological results for the whole group are given in table III. There was no significant difference overall in the prevalence of autoantibodies between the heart-block and control groups. Of the 40 patients whose immunoglobulins were determined 25 were found to have raised IgM levels and 11 raised IgG levels; these increases, however, were not statistically significant.

Discussion

Idiopathic bundle-branch fibrosis is thought to be an end-stage change of damaged Purkinje tissue.⁸ Current hypotheses are that it is secondary to a myopathic process¹ or to a fibrocalcific

ageing change.⁹ Round-cell infiltration was noted in eight out of 62 cases described by Lenègre¹ and has been reported by many others since, but these cells were presumed not to be involved in the pathogenesis of heart block. Zoob and Smith¹⁰ suggested that autoimmunity might be involved in heart block, but this hypothesis was not followed up. Myocarditis has also been implicated.¹¹ Bundle-branch fibrosis is probably not a single disease because similar changes occur in other disorders—for example, familial prolongation of the Q-T interval.¹² Fibrosis selectively replacing the conducting tissue has been produced experimentally as a sequel to a chronic graft rejection reaction in a dog heart homograft.¹³

It is difficult to select a group of patients to study with idiopathic bundle-branch fibrosis. Harris *et al.*² showed that some of these patients have angina without necropsy evidence of coronary stenosis. Either a narrow or the more usually widened QRS complex on the electrocardiogram is compatible with this diagnosis. Chronic heart block has been associated with diabetes,¹ rheumatoid arthritis,¹⁴ and a previous history of diphtheria.¹⁵

To compare the prevalence of autoimmune disease in this group with that in the normal population precise statistics are required. Many of the published surveys are of hospital patients, and these results may exceed those in old people in the community. The prevalence of pernicious anaemia varies with age, sex, race, and geography. It reaches a peak around the 7th to 8th decades. In Britain, Scott¹⁶ found an overall prevalence of 1.27 cases per 1000, with the lowest rates in the south-east (0.6 per 1000), from which area our patients were drawn. A similar survey by Mosbech¹⁷ in Denmark gave a peak prevalence of 3 per 1000 for people aged 60–80 years.

Lloyd and Goldberg¹⁸ found 53 cases of primary hypothyroidism among 3417 geriatric hospital patients—a prevalence of 1.6%. The peak prevalence was in the 6th to 8th decades. This compares with the prevalence of 4% in our series of patients.

Vitiligo occurs in about 1% of the population, with over half of the cases arising before the age of 20. In four of the five cases reported here the disorder had become apparent in adolescence or early adulthood. In one of the largest surveys carried out, Grunnet *et al.*¹⁹ found vitiligo in 1.44% of Danish hospital patients; 3.7% of those with vitiligo also had pernicious anaemia.

The prevalence of thyroglobulin and thyroid microsomal and gastric parietal cell antibodies is dependent on age and sex. In the population studied by Hooper *et al.*²⁰ gastric parietal cell antibodies were detected by immunofluorescence in up to 10% of people aged between 60 and 80 years and thyroid antibodies in up to 12% of cases. About 5% of this age group were positive for rheumatoid factor. The findings in our study of 8% positive for gastric parietal cell antibodies and 7% positive for thyroid microsomal antibodies are usual for this age group. The Fujizaki test, which is more sensitive than immunofluorescence at a 1/10 dilution, gave a positive result in 15% of cases.

In conclusion, therefore, our results suggest an association between vitiligo, primary hypothyroidism, pernicious anaemia, and idiopathic chronic heart block. Specific antibodies to conducting tissue have recently been detected²¹ but it is unlikely that humoral immunity alone is the pathogenic factor in idiopathic heart block.

We wish to thank Professor I. M. Roitt and Professor Deborah Doniach for advice and hospitality in the department of immunology,

Middlesex Hospital. The work was supported by grants from St. George's Hospital Research Fund and the Wellcome Foundation.

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PRELIMINARY COMMUNICATIONS

Free erythrocyte protoporphyrin level and nerve conduction velocity in end-stage renal disease

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British Medical Journal, 1975, **4**, 324-325

Summary

Increased free erythrocyte protoporphyrin concentrations and depressed motor nerve conduction velocities (MNCV) were observed in 45 patients on maintenance haemodialysis. Neither of these findings could be correlated with age, duration or frequency of dialysis, or the degree of uraemia present. A strong negative correlation ($r = -0.53$; $P < 0.001$), however, existed between the free erythrocyte protoporphyrin level and the MNCV, which suggested either (a) a direct effect of iron status on nerve function, or (b) a toxic factor in "uraemia" that depresses both nerve conduction and haemoglobin synthesis activity.

Introduction

There are few published descriptions of abnormalities of haemoglobin precursors in end-stage renal disease. Increased plasma levels of δ -aminolaevulic acid and porphobilinogen were, however, reported by Leber *et al.*¹ in 15 patients. Their findings were consistent with the frequency of anaemia, a common complication of advanced renal insufficiency. Since hepatic porphyrias and uraemia are often associated with clinical or latent neuropathies^{2,3} we were interested in dialysed patients

(a) to measure some haeme precursor abnormalities, and (b) to establish the relation between these abnormalities and motor nerve conduction velocities (MNCV).

Patients and methods

Forty-five patients (27 men and 18 women) with chronic end-stage renal disease on maintenance haemodialysis were investigated. Their ages ranged from 19 to 68 years with a mean of 40.5 years. Altogether 20 had chronic glomerulonephritis, 12 chronic interstitial nephritis, 4 polycystic kidney disease, 6 malignant nephrosclerosis, and 3 other renal diseases. The patients had been dialysed for five to seven hours three times a week for an average of 37 months (range 6-85 months) before the study, a 1.03-m² Cuprophane RP-5 machine being used. All had an internal arteriovenous fistula. Protein intake was not restricted, and the patients received a phosphate binder (aluminium hydroxide), calcium carbonate, and multivitamin preparations. None had hepatitis or clinical evidence of peripheral neuropathy.

Blood chemical values were measured every two weeks, and MNCV of peroneal nerves every two months. All chemical, haematological, and electrical studies reported here were performed the same day before dialysis was begun. Blood urea, creatinine, urate, calcium, phosphate, and electrolytes were measured by standard methods on an AutoAnalyzer, and haemoglobin was measured with a Coulter counter. The Hyland Ferro-Chek II colorimetric test^{4,5} was used for the serum iron and total iron-binding capacity. Free erythrocyte protoporphyrin was determined spectrophotometrically.⁶ The MNCV of peroneal nerves was measured in a warm laboratory (22-23°C), the nerves being stimulated supramaximally with a Racia apparatus and skin electrode. The responses were picked up with skin electrodes and amplified by an electromyograph. The mean of two or more velocities measured was recorded as the value for a given day. Normal values for the investigations are given in the table.

Results

The mean free erythrocyte protoporphyrin level was significantly higher ($P < 0.001$) in the uraemic patients than in a group of normal controls (table), no correlation being observed with age, duration or frequency of dialysis treatment, or the degree of uraemia as assessed biochemically. There was, however, a close correlation between these levels and serum iron ($r = -0.58$; $P < 0.001$), total iron-binding capacity ($r = +0.53$; $P < 0.001$), and transferrin saturation ($r = -0.62$; $P < 0.001$) (fig 1) but no correlation with haemoglobin.

MNCV was significantly decreased ($P < 0.001$) in the uraemic patients (table), no correlation being observed with age, duration or frequency of dialysis treatment, or severity of uraemia. It was, however, closely correlated with the protoporphyrin concentration ($r = -0.53$; $P < 0.001$) (fig 2) but not with serum iron ($r = 0.31$; $P < 0.05$) or transferrin saturation.

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